Enantioselective Hydrogenation of β-Acylamino Acrylates Catalyzed by Rhodium(I)-Monophosphite Complexes

Thomas Jerphagnon,[a] Jean-Luc Renaud,[a] Patrice Demonchaux,[b] Amadéo Ferreira,[b] Christian Bruneau[a,*]

[a] Institut de Chimie de Rennes, UMR 6509: CNRS – Université de Rennes 1, Organométalliques et Catalyse, Campus de Beaulieu, 35042 Rennes Cedex, France
Fax: (+33)-223-236-939, e-mail: Christian.bruneau@univ-rennes1.fr
[b] SEAC-Chimie fine, 145 Chemin des Lilas, 59310 Beuvry-la-Forêt, France
Fax: (+33)-320-646-831, e-mail: patrice.demonchaux@fr.nufarm.com

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Abstract: Chiral rhodium(I) complexes bearing monophosphite ligands, prepared from chiral Binol and (L)-menthol, were found to be efficient catalysts for the asymmetric hydrogenation of β-acylamino acrylates with ee values up to 94%.

Keywords: β-acylamino acrylates; enantioselective catalysis; hydrogenation; monophosphite ligands; rhodium

The preparation of chiral β-amino acid derivatives is an important goal in the pharmaceutical field. They are important building blocks for the synthesis of β-lactams, β-peptide antibiotics and drugs.[1] One of the most attractive and direct pathways to obtain these compounds is the enantioselective hydrogenation of prochiral enamide derivatives with chiral metal complexes. Indeed, interesting results have been obtained with rhodium catalysts containing a bidentate diphosphine ligand such as DuPhos and analogues,[2] Tangphos,[3] BICP,[4] and other optically pure diphosphines.[5]

In the last years, increasing attention has been directed to chiral monophosphites,[6] monophosphonites,[7] and monophosphoramidites,[8] due to their ready accessibilities and their efficiency for the hydrogenation of α-dehydroamino acids and itaconic acid derivatives. Very recently, the use of monophosphoramidites for the hydrogenation of (*Z*)- and (*E*)-β-acylamino acrylates has been reported,[9] but to our knowledge, no phosphite ligand has been used in the enantioselective hydrogenation of β-acylamino acrylates.

We now report the hydrogenation of β-acylamino acrylates catalyzed by rhodium(I)-chiral monophosphite complexes (Scheme 1) and show the crucial role of the binaphthyl moiety in terms of reactivity and enantioselectivity.

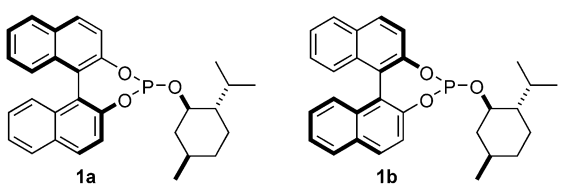
The monophosphite ligands **1** were synthesized in two steps by treatment of (L)-menthol with 1 equivalent of phosphorus trichloride and triethylamine in tetrahydrofuran followed by addition of 1 equivalent of racemic Binol and 2 equivalents of triethylamine. The phosphite diastereoisomers **1a** [(*S*)-binaphthyl, (L)-menthyl] and **1b** [(*R*)-binaphthyl, (L)-menthyl] were separated by successive recrystallisation in ether, at room temperature and 0 °C, respectively.[10]

Complexes **I** $[Rh(\mathbf{1a})_2(COD)]BF_4$ and **II** $[Rh(\mathbf{1b})_2(COD)]BF_4$ were prepared by addition of 2 equivalents of the corresponding ligand **1a** or **1b** to $[Rh(COD)_2]BF_4$ in dichloromethane at room temperature for 1 h. They were isolated in quantitative yield after elimination of the solvent under vacuum and precipitation in ether.

The prochiral derivatives **2a – d** were prepared by reaction of ammonium acetate with the suitable β-ketoester followed by acylation of the amino group.[9] This method afforded the acetamidobut-2-enoates **2a – d** as 1:1 mixtures of (*Z*) and (*E*)-isomers.

The hydrogenation reactions were first performed from **2b** (0.5 mmol) as a (1:1) ethyl (*Z*/*E*)-β-acetylaminobut-2-enoate mixture and 1 mol % of complex **I** (Table 1, Scheme 2).

No conversion was observed when the reactions were performed in an apolar solvent such as toluene. In 2-propanol and ethyl acetate, the catalytic system was active but the enantiomeric excesses did not exceed 21% (entries 1 – 3). The best enantioselectivities and conversions were obtained in dichloromethane (up to 81%, entries 4 – 9). Under only 3 bars of hydrogen at 50 °C a low conversion was observed (only 4%), but a good enantiomeric excess (81%) was obtained. At the same



Scheme 1.

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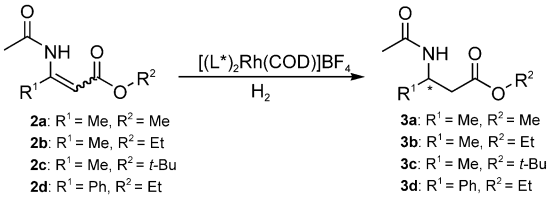

Scheme 2.

reaction temperature, a total conversion was observed under 15 bars but to the detriment of the enantiomeric excess which dropped to 36% (entry 5). The system was optimized under 15 bars of hydrogen at room temperature for 30 h with 71% of conversion and 69% ee. Decreasing the pressure to 10 bars or increasing it to 20 and 30 bars led to lower enantioselectivities.

The hydrogenation with rhodium precatalysts **I** and **II** was extended to various β-acylamino acrylate derivatives. Thus, at 25 °C in dichloromethane under 15 bars H_2 pressure, with the catalyst precursor **I**, the (*Z*)-**2** isomers were hydrogenated faster than the corresponding (*E*)-**2** isomers, but under the same reaction conditions, this better reactivity led to a much lower enantioselectivity (Table 2). Compound (*Z*)-**2b** was obtained in 89% conversion and 38% enantiomeric excess from (*Z*)-**2b**, whereas (*E*)-**2b** led to only 61% conversion but 94% ee (entries 5 and 6). In this latter case, complete conversion of (*E*)-**2a** was obtained in the presence of 2 mol % of precatalyst **I** and the same enantioselectivity (94% ee) was obtained for **3b** (entry 7, Table 2). The bulkiness of the ester moiety had a crucial influence in this hydrogenation process: the *tert*-butyl ester derivative **2c** led to almost no conversion after 30 h of reaction under the conditions which led to good conversion of the methyl **2a** and ethyl **2b** esters.

The hydrogenation carried out with the β-acetylamino β-aryl acrylate **2d** as prochiral substrate and the rhodium complex **I** showed a good conversion (82%) but a modest optical purity (52% ee, entry 9). It is worthy of note that the nature of the R^1 moiety (aryl or alkyl) (Scheme 2) has no major influence as similar reactivities and enantioselectivities were obtained with compounds **2a**, **b** and **2d**.

The use of the chiral monophosphite **1b** (complex **II**), which bears the (*R*)-binaphthyl framework led to a completely different behaviour during the hydrogenation of compounds **2**. As previously reported by Xiao,[6b] the absolute configuration of the Binol group played a crucial role on the configuration of the hydrogenated esters since hydrogenation of β-acylamino acrylates **2a – d** performed with **1a** [(*S*)-naphthyl] as chiral monophosphite ligand provided (*S*)-**3a – d**, whereas monophosphite **1b** [(*R*)-naphthyl] led to (*R*)-**3a – d** as major enantiomers. With the catalyst precursor **II**, not only the reaction was faster from the (*E*)-**2** than from the (*Z*)-**2** derivatives, but the enantioselectivity significantly increased starting from the (*Z*)-**2** derivatives. Indeed, the best enantiomeric excesses were obtained for the hydrogenation of (*Z*)-**2a** (73%, entry 10) and (*Z*)-**2b** (67%, entry 12) isomers. This is in sharp contrast with the previously known results[2–5] obtained with rhodium diphosphine catalysts since the (*E*)-isomer was always reported as providing the best ees. Even though the conversions remained low, the best enantioselectivities resulting from the hydrogenation of the (*Z*)-isomers were obtained with the rhodium complex bearing the phosphite ligands **1b**. Under similar reaction conditions, the conversions of the (*E*)-isomers **2a – c** were independent of the catalyst precursor **I** or **II**. However, when **II** was used as precatalyst, a noticeable "mismatch" effect was observed in terms of conversion from the (*Z*)-isomers as low conversion of compounds (*Z*)-**2a** and **b** and (*Z*)-**2d** were obtained after 30 h of reaction (12, 8 and 9%, respectively), whereas conversions around 80% were obtained when **I** was used (entries 2, 5 and 9,

Table 1. Hydrogenation of a (1:1) mixture of ethyl (E/Z)-acetamidobut-2-enoate **2b** in the presence of the rhodium precatalyst **I**.

Entry	Solvent	P_{H_2} [bars]	T [°C]	t [h]	Conv [%][a]	ee [%][b]
1	*i*-PrOH	10	50	20	92	5
2	EtOAc	5	50	20	88	19
3	EtOAc	10	50	20	97	21
4	CH_2Cl_2	3	50	20	4	81
5	CH_2Cl_2	15	50	30	100	36
6	CH_2Cl_2	10	25	30	49	45
7	CH_2Cl_2	15	25	30	71	69
8	CH_2Cl_2	20	25	30	96	32
9	CH_2Cl_2	30	25	30	100	30

The hydrogenation reactions were carried out with 0.5 mmol of **2b** and 1 mol % of rhodium precatalyst **I** in 5 mL of dichloromethane.

[a] Conversions were determined by ^1H NMR.

[b] Enantiomeric excesses were determined by chiral GC analysis using a Chiraldex β-PM column.

Table 2. Hydrogenation of β-acylamino acrylates **2** in CH_2Cl_2 at 25 °C under 15 bars of hydrogen.

Entry	Complex	Compound	Isomer	Conv [%][a]	ee [%]
1	**I**	**2a**	(*Z*/*E*) (1:1)	72	74-(*S*)[b]
2	**I**	**2a**	(*Z*)	82	55-(*S*)[b]
3	**I**	**2a**	(*E*)	57	91-(*S*)[b]
4	**I**	**2b**	(*Z*/*E*) (1:1)	71	69-(*S*)[b]
5	**I**	**2b**	(*Z*)	89	38-(*S*)[b]
6	**I**	**2b**	(*E*)	61	94-(*S*)[b]
7[c]	**I**	**2b**	(*E*)	100	94-(*S*)[b]
8	**I**	**2c**	(*Z*)	0	–
9	**I**	**2d**	(*Z*)	82	52[d]
10	**II**	**2a**	(*Z*)	12	73-(*R*)[b]
11	**II**	**2a**	(*E*)	56	67-(*R*)[b]
12	**II**	**2b**	(*Z*)	8	67-(*R*)[b]
13	**II**	**2b**	(*E*)	64	40-(*R*)[b]
14	**II**	**2b**	(*Z*/*E*) (1:1)	16	50-(*R*)[b]
15	**II**	**2c**	(*Z*)	2	n.d.
16	**II**	**2d**	(*Z*)	9	3[d]

The hydrogenation reactions were carried out with 0.5 mmol of substrate and 1 mol % of rhodium precatalyst in 5 mL of dichloromethane for 30 h.

[a] Conversions were determined by ^{1}H NMR.

[b] Enantiomeric excesses were determined by chiral GC using a Chiraldex β-PM column.

[c] Hydrogenation carried out with 2% of rhodium precatalyst.

[d] Enantiomeric excesses were determined by chiral GC using a CP Chirasil-Dex CB column; the configuration of the chiral centre was not determined.

Table 2). It is worthy of note that with **II** the ester substituent also had a great impact on the enantioselectivity and that the best excesses were obtained with the methyl ester. These results show that it is difficult to obtain good enantioselectivities for both the (*Z*)- and (*E*)-isomers under similar hydrogenation conditions with the monodentate binaphthyl-menthyl phosphite ligands, as was also observed when phosphoramidites associated to rhodium were used as chiral ligands.[9a]

In conclusion, we have shown that monophosphites **1a** and **1b** are efficient ligands for the rhodium-catalyzed hydrogenation of β-acetylamino acrylates in dichloromethane at room temperature under 15 bars of hydrogen. With this catalytic system, we were able to obtain compounds **3** with ees up to 94% from (*E*)-β-dehydroamino acid esters **2**. We have shown that the binaphthyl fragment [(*R*) or (*S*)] imposes the absolute configuration of the hydrogenated compound **3**, and that it also plays a crucial role in the efficiency of the catalyst and the enantioselectivity of the hydrogenation.

Experimental Section

Typical Procedure for the Rhodium-Catalyzed Enantioselective Hydrogenation of 2a

The β-acylamino acrylate **2a** (0.5 mmol, 1 equiv.) and the chiral precatalyst **I** or **II** (0.005 mmol, 1 mol %) were introduced in a 25 mL stainless steel autoclave under an argon atmosphere. The mixture was degassed by three vacuum-filling argon cycles before adding 5 mL of degassed and distilled dichloromethane. Then, the autoclave was purged three times with hydrogen and the vessel was pressurized to 15 bars. After 30 h at 25 °C, the autoclave was opened and the solvent was removed under reduced pressure. The conversion was determined by ^{1}H NMR analysis of the crude mixture. Subsequently, the residue was purified by chromatography over silica gel, eluted with a 1:1 heptane/diethyl ether mixture.

The enantiomeric excesses were determined by GC using a Chiraldex β-PM column or a CP Chirasil-Dex CB column.

Satisfactory analyses in accordance with published data were obtained by ^{1}H NMR and ^{31}P NMR of the ligands[10] and the organic compounds.[9a]

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